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Vatalanib in malignant mesothelioma: A phase II trial by the Cancer and Leukemia Group B (CALGB 30107)

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Abstract

Introduction—The Cancer and Leukemia Group B (CALGB) conducted a multi-center phase II trial to evaluate the efficacy and safety of vatalanib in previously untreated patients with

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malignant mesothelioma and to evaluate potential biomarkers of disease response (CALGB 30107).

Methods—Treatment consisted of vatalanib 1250 mg given orally once daily. CT scans were obtained at baseline and every 6 weeks thereafter. Baseline serum levels of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), thrombospondin-1 (TSP-1), and mesothelin were obtained. The primary endpoint was 3-month progression-free survival (PFS).

Results—Forty-seven patients enrolled at 19 centers. The median age was 75 years, and the majority of patients (79%) had an ECOG performance status of 1. Tumors were classified as epithelial (77%), sarcomatoid (10%), or mixed (9%) histology. Toxicity was mild; the most common grade 3/4 adverse events were neutropenia (2%), nausea (15%), elevated alanine aminotransferase (11%), hypertension (2%), and gastrointestinal bleeding (2%). Partial responses were observed in 6% of patients and stable disease in 72% of patients. The 3-month PFS rate was 55% (95% CI: 40%, 68%). The median PFS was 4.1 months. Median overall survival was 10.0 months. There was no correlation between serum levels of VEGF, PDGF, TSP-1, or mesothelin and treatment response, PFS, or survival.

Conclusions—Vatalanib as a single agent with this dose and schedule does not warrant further study in this disease.

Keywords

Mesothelioma; clinical trial phase II; vatalanib; VEGF Receptor; PDGFB; molecular targeted therapy

INTRODUCTION

Cytotoxic chemotherapy combinations have achieved the best survival outcomes in patients with malignant mesothelioma (MM), but even the best results realized with these combinations leave room for significant improvement [1-2]. Despite the obvious need for new therapies, progress has been slow largely due to a poor understanding of the biology of MM and an inability to rationally test drugs that employ mechanisms based on molecular targeting. Recent studies have identified several common molecular and genetic abnormalities in MM cells that could potentially be used as targets for novel therapeutic agents. One such drug is vatalanib (PTK 787/ZK222584, Novartis Pharmaceuticals, East Hanover NJ, Schering AG, Germany), an inhibitor of tyrosine kinases associated with two receptors known to be deregulated in MM: vascular endothelial growth factor (VEGF) receptor and the platelet-derived growth factor (PDGF) receptor [3].

VEGF, a potent angiogenic growth factor, is found at high levels in the plasma and tumors of MM patients [4]. VEGF mRNA expression in tumors correlates strongly with microvessel density and poor survival outcomes [3,5]. VEGF is also thought to act as an autocrine growth factor for MM cells through stimulation and binding of the VEGF receptors, flt-1 and KDR [6]. Inhibitors of VEGF can slow the growth of MM in several *in vivo* models [7,8].

The PDGF pathway is also dysregulated in MM. Unlike normal mesothelial cells that express the PDGF- α receptor, MM cells express the PDGF- β receptor [9]. This differential expression suggests that PDGF may act as an autocrine growth factor for MM [10]. Furthermore, PDGF may be a chemo-attractant for MM cells through an interaction between the PDGF receptor and integrin $\alpha 3 \beta 1$ [11]. Karyotypic and comparative genomic hybridization analyses demonstrate that chromosome 22q is frequently damaged in MM patients [12, 13]. Monosomy 22 is of particular interest given that a known tumor suppressor gene (NF2) is present at 22q12. The gene that codes for PDGF (c-sis) is located at 22q13. In experimental models, deregulation of c-sis leads to malignant transformation through the over-production of PDGF [14]; inhibition of PDGF- β receptor mRNA significantly decreases MM growth [15]. These data suggest that inhibiting the VEGF and PDGF pathways could have useful therapeutic consequences for patients with MM

Vatalanib, an inhibitor of several VEGF receptors (KDR, flt-1 and flk-1) and the PDGF receptor, inhibits the growth of several tumor types in animal models [16]. The recommended phase II dose of 1250 mg given orally once daily was administered with FOLFOX chemotherapy in 2 phase III trials in colorectal cancer [17, 18]. Since MM is associated with high VEGF expression and preferential PDGF- β expression, we conducted a phase II multicenter study to evaluate the activity of vatalanib in MM patients.

PATIENTS AND METHODS

Eligibility Criteria

Eligible patients were over 18 years of age with histologically confirmed MM not amenable to curative intent surgery, had unidimensionally measurable disease, and an ECOG performance status of 0-1. No prior systemic chemotherapy was permitted. Prior intrapleural therapy (including sclerosing agents or bleomycin) was allowed. Patients who underwent major surgery or radiotherapy to lesions other than those used for measurement were required to wait 2 or 4 weeks, respectively, before starting treatment. Adequate hematologic, hepatic, and renal function and $< 1+$ proteinuria were required. Each participant signed an IRB approved informed consent in accordance with federal and institutional guidelines

Study evaluations

Baseline evaluation included a history and physical examination, laboratory evaluation, serum for correlative studies, and CT scans completed within 4 weeks of initiating treatment. The study chair reviewed all pathology reports.

A history and physical exam were performed every 21 days. CT scans were obtained every 2 cycles. Patients were evaluated for response according to the modified RECIST criteria of Nowak and Byrne [19]. Confirmatory scans were obtained at least 4 weeks following initial documentation of response.

Treatment

Patients received 1250 mg of vatalanib orally daily. A treatment cycle was defined as continuous therapy for 21 days.

Side effects were graded according to NCI Common Toxicity Criteria version 3.0. Dose adjustments for toxicity were based on a stepwise reduction schedule. Patients whose toxicity did not sufficiently diminish within 14 days were removed from study treatment. Vatalanib doses were not re-escalated once dose reductions occurred.

Correlative Analysis

Circulating markers were assayed on serum drawn within 7 days before starting treatment. Detection of VEGF, PDGF, and thrombospondin-1 (TSP-1) was performed using commercially available ELISA kits (R & D Systems). Mesothelin levels were determined using an ELISA assay provided by Fujirebio Diagnostics. A Cox proportional hazard model was constructed to determine the significant relationships between overall survival (OS), progression-free survival (PFS), and all of the dichotomized serum markers above and below their sample medians. The analysis was repeated with the natural logarithm transformation of the values for the serum markers.

Statistical Analysis

Previous analysis of 10 CALGB MM trials demonstrated a 60% 3-month PFS among good performance status patients [20]. The primary objective of this study was to assess the 3-month PFS rate. Secondary objectives included: estimation of response rate, characterization of toxicity, estimation of OS and PFS, and determination of whether circulating serum levels of VEGF, PDGF, TSP-1, or mesothelin correlated with response to vatalanib. A patient was considered as having been successfully treated if they remained progression-free for 3 months after initial vatalanib administration. Specifically, the hypothesis tested was $H_0: P \leq 0.55$ versus $H_1: P > 0.55$, where P is the proportion of patients who remained progression free for 3 months after initial treatment. The trial was designed as a single-stage study to enroll 40 eligible patients to differentiate a success rate of 55% (null) versus 75% (alternative) with a Type I error rate of 0.10 and a power of 0.90. Kaplan-Meier curves were used to describe OS and PFS [21]. OS was defined as the time between registration and death, and PFS as the time between registration and disease progression or death.

RESULTS

Patient characteristics

Forty-seven patients at 19 centers enrolled in this study between July 2003 and November 2004. Patient characteristics are summarized in Table 1. The median age was 75 years (range 51-92), and 64% of the patients were over 70. Nearly all (91%) of the patients were male, consistent with an occupationally-induced cancer. Most (79%) had an ECOG performance status of 1. Epithelial histology was present in 77% of patients.

The median number of treatment cycles was 3 (range 1-40).

Response and Toxicity

All patients were evaluable for toxicity assessment, and 46 for response. One patient died during the first treatment cycle from disease progression prior to being assessed for response.

A partial response was observed in 3 patients, for an objective response rate of 6.4% (95% CI 1.3%-17.5%). Stable disease occurred in 34 patients (72.3%). The median PFS was 4.1 months (95% CI 2.2–5.3). The PFS rate at 3 months, which was the primary endpoint of this study, was 55.3% (95% CI 40.1%-68.1%). The median OS was 10.0 months (95% CI 6.3–14.4). The one-year survival rate was 44.7%. Figure 1 depicts the Kaplan-Meier progression-free and overall survival curves.

Table 2 lists treatment-related grade 3 and higher toxicities. Vatalanib was generally well tolerated in this elderly population. There were no treatment-related grade 5 events. The most common non-hematologic grade 3/4 adverse events were nausea (15%), vomiting (9%), ALT elevations (11%), and AST elevations (6%). Only one patient (2%) experienced grade 3 hypertension and no patient experienced hypertension greater than grade 3.

Biomarkers

Forty patients had adequate serum samples submitted for analysis. We carried out a Cox proportional model analysis of the relationship of baseline serum PDGF, VEGF, TSP-1 and mesothelin levels with OS, PFS, and treatment response. Serum levels were initially defined as binary variables according to whether the values were above or below corresponding medians. Wald tests on the estimated hazard ratios failed to show significant associations between any of the biomarkers and OS or PFS. Regression analysis was performed with biomarkers defined as continuous covariates. Natural logarithm transformations were made to reduce the skewness of the covariate distribution. Again, no significant associations were found, with or without adjusting for baseline covariates. Similarly, none of these biomarkers predicted for tumor response.

DISCUSSION

This phase II trial of vatalanib in chemo-naïve patients with advanced MM resulted in treatment outcomes that compare favorably with the results of previous trials of both single-agent cytotoxic chemotherapy and several cytotoxic doublets, with less toxicity [1,2]. The primary objective of this study was not met, however, as the 3-month PFS of 55.3% (95% CI 40.1-68.1) fell short of the protocol-specified 75% to warrant further investigation. Given the minimal toxicity profile of vatalanib in this elderly population, it is likely that vatalanib could be successfully combined with chemotherapy.

In designing this phase II study, we decided to use a 3-month PFS rate as the primary endpoint because it was more likely to be representative of efficacy for a cytostatic agent compared to more traditional radiographic response criteria or OS. In retrospect, a 6-month PFS endpoint may have been more clinically meaningful. We selected a 75% PFS rate based on an analysis of ten CALGB trials conducted since 1984, covering over 330 patients with demographics, performance status, and clinical characteristics comparable to our present population [20]. The median 3-month PFS rate in this CALGB analysis was 60%. More recently, the European Organization for Research and Treatment of Cancer (EORTC) analyzed their 523 patient database from ten completed mesothelioma trials, and determined PFS timepoints for agents deemed to have significant, moderate, or insufficient clinical activity [22]. Our observed 3-month PFS rate of 55.3% falls between their values for a

moderately active agent (3 month PFS 59%) and one that is insufficiently active (3-month PFS 52%).

We chose a dose of 1250 mg as a single daily dose based on available pharmacokinetic data at the time the study was designed. Subsequent information suggests that a dose of at least 1000 mg twice daily is optimal for biologic activity [23]; our results might have been more favorable with a twice-daily dosing schedule. It should be noted that we did not observe the degree of hypertension typically associated with agents that target the VEGF axis, thus supporting the notion that 1250 mg as a single daily dose may have been insufficient to exert a significant biologic effect.

Preclinical evidence implicating the PDGF- β and VEGF pathways in the evolution and growth of MM suggested that interfering with these pathways could yield tangible clinical benefits in MM patients. The available clinical evidence to date, including the present study, seems to call into question the actual *in vivo* importance of these targets for MM, the ability of current agents to effectively disrupt these targets, or the adequacy of the biomarkers used to monitor these molecular pathways. Numerous drugs that target these pathways have been tested in MM, with very modest results [1-3, 24].

In conclusion, further development of vatalanib as a single agent for patients with MM is not warranted based on the findings of the present study. However, given its lack of substantial toxicity and moderate clinical benefit, it might be worth re-exploring this agent dosed twice daily or in combination with cytotoxic chemotherapy. Future clinical investigations of vatalanib and similar agents in MM should also investigate whether the expected molecular targets are biologically active.

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Figure 1.
Kaplan-Meier Survival Curves for Progression-Free Survival and Overall Survival

Table 1

Patient Characteristics

Characteristics	N = 47 (%)
Gender	
Male	43 (91)
Female	4 (9)
Median age (range)	75 (51-92)
Histology	
Epithelial	36 (77)
Sarcomatoid	5 (10)
Mixed Subtype	4 (9)
Unknown	2 (4)
Site of Origin	
Pleura	41 (88)
Peritoneum	3 (6)
Other	3 (6)
Weight Loss	
<10%	24 (51)
>10%	22 (47)
Unknown	1 (2)
ECOG performance status	
0	10 (21)
1	37 (79)
Baseline platelet count	
Above 400k	18 (38)
Below 400k	29 (62)
Baseline WBC count	
Above $8.3 \times 10^9/l$	24 (51)
Below $8.3 \times 10^9/l$	23 (49)

Table 2

Grade 3/4 toxicities (N=47)

Toxicity	Grade 3 (%)	Grade 4(%)
Hematological		
Granulocytopenia	0 (0)	1 (2)
Lymphopenia	1 (2)	0 (0)
Non hematological		
Nausea	6 (13)	1 (2)
Vomiting	4 (9)	0 (0)
Fatigue/Asthenia	2 (4)	0 (0)
ALT elevation	4 (9)	1 (2)
AST elevation	2 (4)	1 (2)
Dyspnea	2 (4)	0 (0)
Hypertension	1 (2)	0 (0)
Neurologic		
Syncope	1 (2)	0 (0)
Confusion	1 (2)	0 (0)